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NEW COMPOUNDS

TECHNICAL FIELD

The present invention relates to novel compounds, and pharmaceutically acceptable salts thereof, which inhibit basic carboxypeptidases, more specifically carboxypeptidase U, and thus can be used in the prevention and treatment of diseases wherein inhibition of carboxypeptidase U is beneficial. In further aspects, the invention relates to compounds of the invention for use in therapy; to processes for preparation of such new compounds; to pharmaceutical compositions containing at least one compound of the invention, or a pharmaceutically acceptable salt thereof, as active ingredient; and to the use of the active compounds in the manufacture of medicaments for the medical use indicated above.

BACKGROUND ART

Fibrinolysis is the result of a series of enzymatic reactions resulting in the degradation of fibrin by plasmin. The activation of plasminogen is the central process in fibrinolysis. The cleavage of plasminogen to produce plasmin is accomplished by the plasminogen activators, tissue-type plasminogen activator (t-PA) or urokinase-type plasminogen activator (u-PA). Initial plasmin degradation of fibrin generates carboxy-terminal lysine residues that serves as high affinity binding sites for plasminogen. Since plasminogen bound to fibrin is much more readily activated to plasmin than free plasminogen this mechanism provides a positive feedback regulation of fibrinolysis.

One of the endogenous inhibitors to fibrinolysis is carboxypeptidase U (CPU). CPU is also known as plasma carboxypeptidase B, active thrombin activatable fibrinolysis inhibitor (TAFIa), carboxypeptidase R and inducible carboxypeptidase activity. CPU is formed during coagulation and fibrinolysis from its precursor proCPU by the action of proteolytic enzymes *e.g.* thrombin, thrombin-thrombomodulin complex or plasmin. CPU cleaves basic amino acids at the carboxy-terminal of fibrin fragments. The loss of carboxy-terminal

lysines and thereby of lysine binding sites for plasminogen then serves to inhibit fibrinolysis.

By inhibiting the loss of lysine binding sites for plasminogen and thus increase the rate of plasmin formation, effective inhibitors of carboxypeptidase U would be expected to facilitate fibrinolysis.

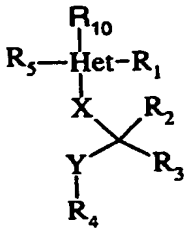
2-mercaptomethyl-3-guanidinoethylthiopropanoic acid is reported as a carboxypeptidase N inhibitor. More recently, this compound has been shown to inhibit CPU, Hendriks, D. *et al.*, Biochimica et Biophysica Acta, 1034 (1990) 86-92.

Guanidinoethylmercaptosuccinic acid is reported as a carboxypeptidase N inhibitor. More recently, this compound has been shown to inhibit CPU, Eaton, D. L., *et al.*, The Journal of Biological Chemistry, 266 (1991) 21833-21838.

DISCLOSURE OF THE INVENTION

It has surprisingly been found that compounds of the Formula I are particularly effective as inhibitors of carboxypeptidase U and thereby useful as medicaments for the treatment or profylaxis of conditions wherein inhibition of carboxypeptidase U is beneficial.

In one aspect, the invention thus relates to compounds of the general Formula I,



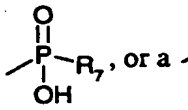
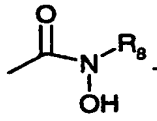
(I)

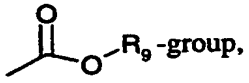
or a pharmaceutically acceptable salt thereof, wherein

R_1 represents H, OH, halogen, C_1-C_6 alkyl, C_1-C_6 alkylaryl, C_1-C_6 alkoxy, cyano, NO_2, SH och $N(R_8)_2$ or CO-C_1-C_6 alkyl,

R_2 represents H, OH, halogen, or C_1-C_6 alkyl,

R_3 represents $COOR_6$, SO_2R_6, SO_3R_6, $P{=}O(OR_6)_2$, $B(OR_6)_2$, $P{=}OR_6(OR_6)$, tetrazole or any carboxylic acid isostere,

R_4 represents  , or a  -group, or a

 -group,

R_5 represents H, OH, halogen, C_1-C_6 alkyl, C_1-C_6 alkylaryl, C_1-C_6 alkoxy, cyano, NO_2, SH och $N(R_8)_2$ or CO-C_1-C_6 alkyl,

R_6 represents H, or C_1-C_6 alkyl, C_1-C_6 alkylaryl, or aryl

R_7 represents a dipeptid or an aminoacid residue, both optionally N-protected,

R_8 represents H, C_1-C_6 alkyl, or C_1-C_6 alkylaryl,

R_9 represents H, or C_1-C_6 alkyl, C_1-C_6 alkylaryl, or aryl

R_{10} represents H, OH, halogen, C_1-C_6 alkyl, C_1-C_6 alkylaryl, C_1-C_6 alkoxy, cyano, NO_2, SH och $N(R_8)_2$ or CO-C_1-C_6 alkyl,

X represents O, S, CH_2, CH_2CH_2, $CH_2CH_2CH_2$, NH, CH(Z) or N(Z),

Y represents O, CH_2, or CH(Z), or a single bond,

Z represents C_1-C_6 alkyl, or C_1-C_6 alkylaryl, and

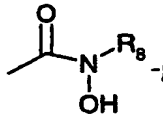
Het represents a 4-, 5-, or 6-membered aromatic or alifatic heterocyclic group containing at least one nitrogen, oxygen or sulphur atom, a 4-, 5-, or 6-membered aromatic or alifatic carbocyclic group or a single bond.

Preferred compounds according to the present invention are those of formula I, or a pharmaceutically accepteble salt thereof, wherein

R_1 represents H, or NH_2,

R_2 represents H,

R_3 represents $COOR_6$,

R_4 represents a  -group,

R_5 represents H, or NH_2,

R_6 represents H, or C_1-C_6 alkyl,

R_8 represents H, C_1-C_6 alkyl, or C_1-C_6 alkylaryl,

R_{10} represents H, or NH_2,

X represents CH_2, CH_2CH_2, or $CH_2CH_2CH_2$,

Y represents a single bond, and

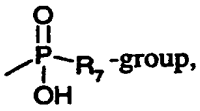
Het represents pyridyl or piperidinyl.

Other preferred compounds according to the present invention are those of formula I, or a pharmaceutically accepteble salt thereof, wherein

R_1 represents NH_2, or a guanidino group,

R_2 represents H,

R_3 represents $COOR_6$,

R_4 represents a  -group,

R_5 represents NH_2, or a guanidino group,

R_6 represents H, or C_1-C_6 alkyl,

R_7 represents a dipeptid or an aminoacid residue, both optionally N-protected,

R_{10} represents NH_2, or a guanidino group,

X represents CH_2, CH_2CH_2, or $CH_2CH_2CH_2$,

Y represents O, and

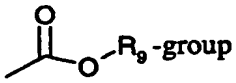
Het represents a single bond.

Yet other preferred compounds according to the present invention are those of formula I, or a pharmaceutically accepteble salt thereof, wherein

R_1 represents H, or NH_2,

R_2 represents H,

R_3 represents $COOR_6$,

R_4 represents a  -group

R_5 represents H, or NH_2,

R_6 represents H, or C_1-C_6 alkyl,

R_9 represents H, or C_1-C_6 alkyl,

R_{10} represents H, or NH_2,

X represents CH_2, or CH_2CH_2,

Y represents CH_2, or a single bond, and

Het represents pyridyl or piperidinyl.

The following definitions shall apply throughout the specification and the appended claims:

The term "C_1–C_6 alkyl" denotes a straight or branched, substituted or unsubstituted, alkyl group having from 1 to 6 carbon atoms. Examples of said lower alkyl include, but is not limited to methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, t-butyl and straight- and branched-chain pentyl and hexyl.

The term "C_1-C_6 alkoxy" denotes a group O-alkyl, wherein alkyl is as defined above

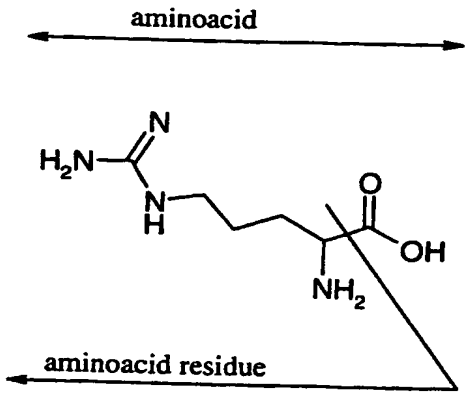
The term "4-, 5-, or 6-membered aromatic or alifatic heterocyclic group containing at least one nitrogen, oxygen or sulphur atom" includes, but is not limited to substituted or unsubstituted azetidine, furan, thiophene, pyrrole, pyrroline, pyrrolidine, dioxolane, oxathiolane, oxazolane, oxazole, thiazole, imidazole, imidazoline, imidazolidine, pyrazole, pyrazoline, pyrazolidine, isoxazole, isothiazole, oxadiazole, furazan, triazole, thiadiazole,

pyran, pyridine, pipridine, dioxane, morpholine, dithiane, oxathiane, thiomorpholine, pyridazine, pyrimidine, pyrazine, piperazine, triazine, thiadiazine, dithiazine groups, and shall be understood to include all isomers of the above identified groups. The term "azetidinyl" shall for example by understood to include the 2-, and 3-isomers and the terms "pyridyl" and "piperidinyl" shall for example by understood to include the 2-, 3-, and 4-isomers.

The term "4-, 5-, or 6-membered aromatic or alifatic carbocyclic group" includes, but is not limited to substituted or unsubstituted phenyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, cyclopentadienyl, cyclohexadienyl groups

The term "halogen" includes fluoro, chloro, bromo and iodo groups.

The term "dipeptide or aminoacid residue" denotes a dipeptid a aminoacid excluding the C-terminal carboxyl group. An illustrative non-limiting example is shown below;



The term "aryl" denotes a substituted or unsubstituted C_6–C_{14} aromatic hydrocarbon and includes, but is not limited to, benzene, naphtalene, indene, antracene, fenantrene, and fluorene

The term "substituted" denotes an C_1-C_6 alkyl, C_1-C_6 alkylaryl or aryl group as defined above which is substituted by one or more alkyl, alkoxy, halogen, amino, thiol, nitro, hydroxy, acyl or cyano groups.

Abbreviations

Ac = acetate

aq = aqueous

AIBN = α,α´-azoisobutyronitrile

Bn = benzyl

Bu = butyl

Bz = benzoyl

DCC = dicyclohexylcarbodiimide

DIAD = diisopropyl azodicarboxylate

DIPEA = diisopropylethylamine

DMAP = N,N-dimethyl amino pyridine

DME = 1,2-dimethoxyethane

DMF = dimethylformamide

DMSO = dimethylsulfoxide

EDC = 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide

Et = ethyl

EtOAc = ethyl acetate

EtOH = ethanol

h = hs

HOAc = acetic acid

HOBt = 1-hydroxybenzotriazol

HPLC = high performance liquid chromatography

KHMDS = potassium bis(trimethylsilyl)amide

LDA = lithium diisopropylamide

Me = methyl

MeOH = methanol

min = minutes

PMB = 4-methoxybenzyl

Ph = phenyl

Pr = propyl

PyBOP = (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate

TEA = trietylamine

TFA = TFA

THF = tetrahydrofuran

Tos = toluene-4-sulfonyl

Both the pure enantiomers, racemic mixtures and unequal mixtures of two enantiomers are within the scope of the present invention. It should also be understood that all the diastereomeric forms possible are within the scope of the invention. Also included in the invention are derivatives of the compounds of the Formula I which have the biological function of the compounds of the Formula I, such as prodrugs.

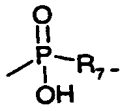
Depending on the process conditions the compounds of the Formula I are obtained either in neutral or salt form and are all within the scope of the present invention.

It will be appreciated by those skilled in the art that the number of possible substituents on Het when "Het represents a 4-, 5-, or 6-membered aromatic or alifatic heterocyclic group containing at least one nitrogen, oxygen or sulphur atom or a 4-, 5-, or 6-membered aromatic or alifatic carbocyclic group" will vary from one structure to another. Also within the scope of the present invention are compounds of the formula I, which contains a multiplicity of substituents on Het chosen within the definitions of R^1,R^5 and R^6 of figure I.

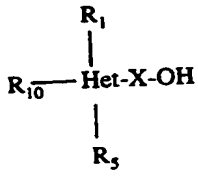
Preparation

The present invention also provides the process A-C for the manufacture of compounds with the general Formula I.

Process A

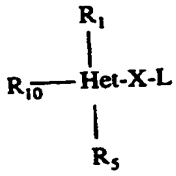
Process A for manufacture of compounds with the general Formula I, wherein R_1, R_5, R_6, R_7, R_{10}, Z and Het are as defined above and R_2 is H, R_3 is $COOR_6$, R_4 is a  group, X is CH_2, CH_2CH_2, $CH_2CH_2CH_2$, Y is CH_2 or CH(Z), comprises the following steps:

a) Compounds of the general formula II



II

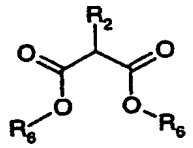
wherein R_1, R_5, R_{10}, X and Hetare as defined for Formula I, which are either commercially available or are available using known techniques, can be converted into a compound of the general formula III,



III

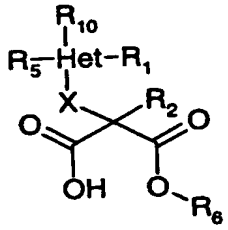
wherein L is a suitable leaving group, such as a chloro, bromo, iodo, triflate or tosyl group, under standard conditions using a suitable reagent, such as PPh_3/CBr_4, TosCl/pyridine or $(CF_3SO_2)_2O$/TEA).

b) Compounds of the general formula III can thereafter be reacted with compounds of the general formula IV



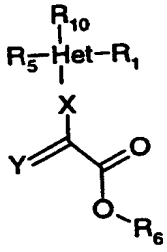
IV

wherein R_2 and R_6 are as defined for Formula I,which are either commercially available or are available using known technics, in the presence of a suitable base, such as K_2CO_3 or NaH, under standard conditions to give compounds of the general formula V.



V

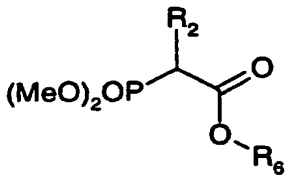
c) Compounds of the general formula V can thereafter be converted to compounds of the general formula VI



VI

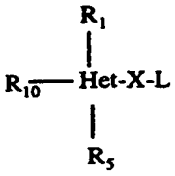
by treatment with formaldehyd in the presence of a suitable base, such as Et_2NH, under standard conditions.

However, if Y is CH(Z) then compounds of the general formula VI can be prepared by treating compounds of the general formula VII



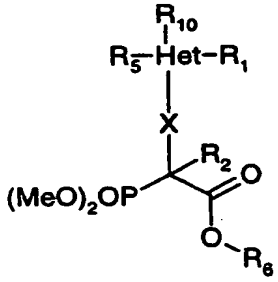
VII

wherein R_2 and R_6 are as defined for Formula I,with an alkylating agent of the general formula III



III

in the presence of a suitable base, such as LDA or NaH, under standard conditions to give compounds of the general formula VIII

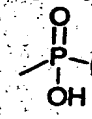


VIII

Compounds of the general formula VIII can thereafter be reacted with an appropriate aldehydeCHO(Z), wherein Z is as defined for Formula I, in the presence of a suitable base, such as KOtBu, LDA or NaH, under standard conditions to give to give a compound of the general formula VI.

d) Compounds of the general formula VI can be further reacted with compounds of the general formula IX

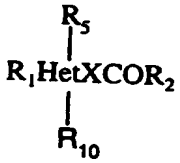
$$R_7PO_2H_2 \qquad IX$$

wherein R_7 is as defined in figure I, in the presence of a suitable reagent, such as BTSP or HMDS, under standard conditions to give compounds of the general formula I, wherein R_1, R_5, R_6, R_7, R_{10}, Z and Het are as defined above and R_2 is H, R_3 is $COOR_6$, R_4 is a  -group, X is CH_2, CH_2CH_2, $CH_2CH_2CH_2$, Y is CH_2 or CH(Z).

Process B

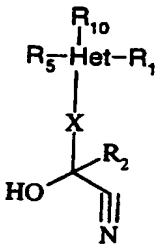
Process B for manufacture of compounds with the general Formula I, wherein R_1, R_2, R_3, R_5, R_6, R_7, R_{10}, Z and Het are as defined above, X is CH_2, CH_2CH_2, $CH_2CH_2CH_2$, Y is O, and R_4 is a  -group, comprises the following steps:

a) Reacting a compound of the general Formula X



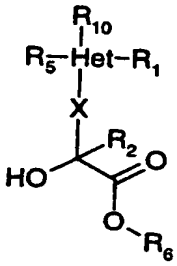
X

wherein R_1, R_2, R_5, R_{10} and Het are as defined in formula I and X is a single bond, CH_2 CH_2CH_2, or $CH_2CH_2CH_2$ in the presence of suitable reagents, such as TMSCN/ZnI_2 or KCN/HOAc, under standard conditions to give compounds of the general formula XI



XI

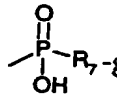
b) Compounds of the general formula XI can thereafter be treated with suitable reagents, such as HCl or HCl/MeOH, under standard conditions to give compounds of the general formula XII



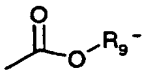
XII

c) Compounds of the general formula XII can thereafter be reacted with compounds of the general formula XIII,

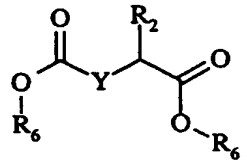
$$R_7PO_3H_2 \qquad \text{XIII}$$

wherein R_7 is as defined in figure I, which are either commercially available, well known in the litterature, or are available using known techniques, in the presence of suitable coupling reagents such a DCC/DMAP, PyBop/DIPEA or $SOCl_2$, under standard conditions to give as compounds of the general formula I, wherein R_1, R_2, R_3, R_5, R_6, R_7, R_{10}, Z and Het defined above, X is CH_2, CH_2CH_2, $CH_2CH_2CH_2$, Y is O and R_4 is a  -group.

Process C

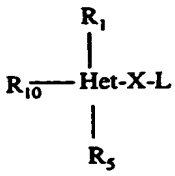
Process C for manufacture of compounds with the general Formula I, wherein R_1, R_2, R_5, R_6, R_9,R_{10}, X, Y, Z and Het are as defined above, R_3 is $COOR_6$ and R_4 is a  group, comprises the following steps

a) reacting a compound of the general formula XIV



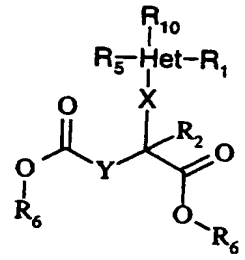
XIV

wherein R_2 and R_6 are as defined in formula I and Y is CH_2, CH(Z), or a single bond, which are either commercially available, well known in the litterature, or are available using known techniques, with a compound of the general formula III

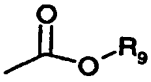


III

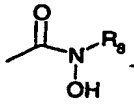
wherein R_1, R_5, R_{10} and Het are as defined for formula I, X is CH_2, CH_2CH_2 or $CH_2CH_2CH_2$ and L is a suitable leaving group, such as Cl, Br, I or tosyl, in the presence of a suitable base, such as LDA or NaH under standard conditions, to give a compound of the general formula XV,



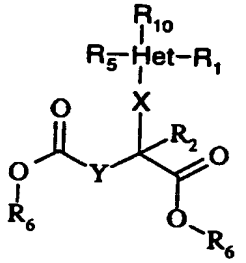
XV

b) hydrolysing a compound of the general formula XV, for example by treatment with aqueous NaOH or aqueous TFA under standard conditions to give compound of the general formula I, wherein R_1, R_2, R_5, R_6, R_9, R_{10}, X, Y, Z and Het are as defined above, and R_3 is $COOR_6$ and R_4 is a  -group.

Process D

Process D for manufacture of compounds with the general Formula I, wherein R_1, R_2, R_5, R_6, R_8, R_{10}, X, Z and Het are as defined above, Y is a single bond, R_3 is $COOR_6$, and R_4 is a  -group, comprises the following steps:

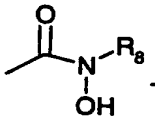
a) Compounds of the general formula XV



XV

can be reacted with compounds of the general formula XVI

HR_8NOH XVI

wherein R_8 is as defined in formula 1, in the presence of suitable reagents, such as DCC/DMAP, under standard conditions, to give compounds of the general formula I, wherein R_1, R_2, R_5, R_6, R_8, X, Z and Het are as defined above, Y is a single bond, R_3 is $COOR_6$, and R_4 is a  -group

It will be appreciated by those skilled in the art that in the process described above the functional groups of intermediate compounds may need to be protected by protecting groups.

Functional groups which it is desirable to protect include hydroxy, amino, mercapto and carboxylic acid. Suitable protecting groups for hydroxy include trialkylsilyl or diarylalkylsilyl (e.g. t-butyldimethylsilyl, t-butyldiphenylsilyl or trimethylsilyl), tetrahydropyranyl and benzyl. Suitable protecting groups for amino, amidino and guanidino include t-butyloxycarbonyl or benzyloxycarbonyl. Suitable protecting groups for mercapto include CO-C_{1-6} alkyl, p-methoxybenxyl and trityl. Suitable protecting groups for carboxylic acid include C_{1-6} alkyl or benzyl esters.

Protecting groups may be removed in accordance with techniques which are well known to those skilled in the art and as described hereinafter.

Certain protected derivatives of compounds of formula I, which may be made prior to a final deprotection stage to form compounds of formula I, are novel.

The use of protecting groups is described in 'Protective Groups in Organic Synthesis', 2nd edition, T.W. Greene & P.G.M. Wutz, Wiley-Interscience (1991). The protective group may also be a polymer resin such as Wang resin or a 2-chorotrityl chloride resin.

It will also be appreciated by those skilled in the art, although such protected derivatives of compounds of formula I may not possess pharmacological activity as such, they may be administered parenterally or orally and thereafter metabolised in the body to form compounds of the invention which are pharmacologically active. Such derivatives may therefore be described as "prodrugs". All prodrugs of compounds of formula I are included within the scope of the invention.

Pharmaceutical formulations

In yet a further aspect, the invention relates to pharmaceutical compositions containing at least one compound of the present invention, or a pharmaceutically acceptable salt thereof, as active ingredient.

For clinical use, the compounds of the invention are formulated into pharmaceutical formulations for oral, intravenous, subcutaneous, tracheal, bronchial, intranasal, pulmonary, transdermal, buccal, rectal, parenteral or other mode of administration. The pharmaceutical formulation contains a compound of the invention in combination with one or more pharmaceutically acceptable ingredients. The carrier may be in the form of a solid, semi-solid or liquid diluent, or a capsule. These pharmaceutical preparations are a further object of the invention. Usually the amount of active compounds is between 0.1–95% by weight of the preparation.

In the preparation of pharmaceutical formulations containing a compound of the present invention the compound selected may be mixed with solid, powdered ingredients, such as lactose, saccharose, sorbitol, mannitol, starch, amylopectin, cellulose derivatives, gelatin, or another suitable ingredient, as well as with disintegrating agents and lubricating agents

such as magnesium stearate, calcium stearate, sodium stearyl fumarate and polyethylene glycol waxes. The mixture may then be processed into granules or pressed into tablets.

Soft gelatine capsules may be prepared with capsules containing a mixture of the active compound or compounds of the invention, vegetable oil, fat, or other suitable vehicle for soft gelatine capsules. Hard gelatine capsules may contain granules of the active compound. Hard gelatine capsules may also contain the active compound in combination with solid powdered ingredients such as lactose, saccharose, sorbitol, mannitol, potato starch, corn starch, amylopectin, cellulose derivatives or gelatine.

Dosage units for rectal administration may be prepared (i) in the form of suppositories which contain the active substance mixed with a neutral fat base; (ii) in the form of a gelatine rectal capsule which contains the active substance in a mixture with a vegetable oil, paraffin oil or other suitable vehicle for gelatine rectal capsules; (iii) in the form of a ready-made micro enema; or (iv) in the form of a dry micro enema formulation to be reconstituted in a suitable solvent just prior to administration.

Liquid preparations may be prepared in the form of syrups or suspensions, e.g. solutions or suspensions containing the active ingredient and the remainder consisting, for example, of sugar or sugar alcohols and a mixture of ethanol, water, glycerol, propylene glycol and polyethylene glycol. If desired, such liquid preparations may contain colouring agents, flavouring agents, preservatives, saccharine and carboxymethyl cellulose or other thickening agents. Liquid preparations may also be prepared in the form of a dry powder to be reconstituted with a suitable solvent prior to use.

Solutions for parenteral administration may be prepared as a solution of a compound of the invention in a pharmaceutically acceptable solvent. These solutions may also contain stabilizing ingredients and/or buffering ingredients. Solutions for parenteral administration may also be prepared as a dry preparation to by reconstituted with a suitable solvent before use.

The typical daily dose of the active substance varies within a wide range and will depend on various factors such as for example the individual requirement of each patient, the route of administration and the disease. In general, oral and parenteral dosages will be in the range of 0.1 to 1000 mg per day of active substance.

Medical and pharmaceutical use

The compounds of the invention are inhibitors of carboxypeptidase U either as such or, in the case of prodrugs, after administration. The compounds of the invention are thus expected to be useful in those conditions where inhibition of carboxypeptidase U is beneficial, such as in the treatment or prophylaxis of thrombosis and hypercoagulability in blood and tissues of mammals, including man.

It is known that hypercoagulability may lead to thrombo-embolic diseases. Conditions associated with hypercoagulability and thrombo-embolic diseases which may be mentioned include protein C resistance and inherited or aquired deficiences in antithrombin III, protein C, protein S and heparin cofactor II. Other conditions known to be associated with hypercoagulability and thrombo-embolic disease include circulatory and septic shock, circulating antiphospholipid antibodies, homocysteinami, heparin induced thrombocytopenia and defects in fibrinolysis. The compounds of the invention are thus indicated both in the therapeutic and/or prophylactic treatment of these conditions. The compounds of the invention are further indicated in the treatment of conditions where there is an undesirable excess of proCPU/CPU.

Particular disease states which may be mentioned include the therapeutic and /or prophylactic treatment of venous thrombosis and pulmonary embolism, arterial thrombosis (e.g. in myocardial infarction, unstable angina, thrombosis-based stroke and peripheral arterial thrombosis) and systemic embolism usually from the atrium during arterial fibrillation or from the left ventricle after transmural myocardial infarction.

Moreover, the compounds of the invention are expected to have utility in prophylaxis of re-occlusion and restenosis (*i.e.* thrombosis) after thrombolysis, percutaneous trans-luminal angioplasty (PTA) and coronary bypass operations; the prevention of re-thrombosis after microsurgery and vascular surgery in general.

Further indications include the therapeutic and/or prophylactic treatment of disseminated intravascular coagulation caused by bacteria, multiple trauma, intoxication or any other mechanism, fibrinolytic treatment when blood is in contact with foreign surfaces in the body, such as vascular grafts, vascular stents, vascular catheters, mechanical and biological prosthetic valves or any other medical device, and fibrinolytic treatment when blood is in contact with medical devices outside the body, such as during cardiovascular surgery using a heart-lung machine or in haemodialysis.

The compounds of the invention may also be combined and/or coadministered with any antithrombotic agent with a different mechanism of action, such as the antiplatelet agents acetylsalicylic acid ticlopidine, clopidogrel, thromboxane receptor and/or synthetase inhibitors, fibrinogen receptor antagonists, prostacyclin mimetics and phosphodiesterase inhibitors and ADP-receptor (P2T) antagonists and thrombin inhibitors.

The compounds of the invention may further be combined and/or coadministered with thrombolytics such as tissue plasminogen activator (natural, recombinant or modified), streptokinase, urokinase, prourokinase, anisoylated plasminogen-streptokinase activator complex (APSAC), animal salivary gland plasminogen activators, and the like, in the treatment of thrombotic diseases, in particular myocardial infarction and stroke.

In vitro experiments

The inhibiting effect of the compounds of the present invention was estimated using the assay described in: Dirk Hendriks, Simon Scharpé and Marc van Sande, Clinical

Chemistry, 31, 1936-1939 (1985); and Wei Wang, Dirk F. Hendriks, Simon S. Scharpé, The Journal of Biological Chemistry, 269, 15937-15944 (1994).

EXAMPLES

General Experimental Procedures

Mass spectra were recorded on a Finnigan MAT TSQ 700 triple quadropole mass spectrometer equipped with an electrospray interface (FAB-MS) and VG Platform II mass spectrometer equipped with an electrospray interface (LC-MS). ^{1}H NMR and ^{13}C NMR measurements were performed on Varian UNITY plus 400, 500 and 600 spectrometers, operating at ^{1}H frequencies of 400, 500 and 600 MHz respectively. Chemical shifts are given in ppm with the solvent as internal standard. Organic extracts were dried using $MgSO_4$ or Na_2SO_4 as the drying agent. Chromatography separations were performed using Merck Silica gel 60 (0.063-0.200 mm). HPLC separations were performed on a HIGHCROM KR100-10C8 column.

Example 1

5-Amino-2-[(1-benzyloxycarbonylamino-2-methyl-propyl)-hydroxy-phosphinoyloxy]-pentanoic acid

(a) 5-*tert*-Butoxycarbonylamino-2-hydroxy-pentanoic acid

Di-*t*-butyl dicarbonate (30.8 g, 0.141 mol) was added in portions during 5 min. to a solution of

5-amino-2-hydroxy-pentanoic acid (17.0 g, 0.128 mol) in 0.5 M NaOH (240 mL) and dioxan (240 mL) at 5 °C. The mixture was stirred for 2.5 h at room tempetrature. During this time 0.5 M NaOH was added to maintain pH 9-10. The dioxan was removed under reduced pressure and the aqueous phase was washed with diethyl ether. The aqueous phase was acidified to pH 2-3 with $KHSO_4$ and extracted with ethyl acetate (3 x 300 mL). The pooled organic phases was washed with water and brine, dried and concentrated under

reduced pressure to give crude 5-*tert*-butoxycarbonylamino-2-hydroxy-pentanoic acid (22.0 g, 73.7%).

(b) 5-*tert*-Butoxycarbonylamino-2-hydroxy-pentanoic acid methyl ester

A solution of methyl iodide (11.5 mL, 0.189 mol) in DMF (50 mL) was added dropwise during 15 min. to a mixture of 5-*tert*-butoxycarbonylamino-2-hydroxy-pentanoic acid (22.0 g, 94.4 mmol) and $NaHCO_3$ (11.8 g, 141 mmol) in DMF (150 mL). After stirring over night, water was added and the mixture was extracted with ethyl acetate. The pooled organic phases was washed with water and brine, dried and concentrated under reduced pressure. The crude product was purified using chromathography (heptane/ethyl acetate, 1:1) to give 5-*tert*-butoxycarbonylamino-2-hydroxy-pentanoic acid methyl ester 9.9 g, 42.5 %)

(c) 2-[(1-Benzyloxycarbonylamino-2-methyl-propyl)-methoxy-phosphinoyloxy]-5-*tert*-butoxycarbonylamino-pentanoic acid methyl ester

A solution of PyBOP (2.1 g, 4.0 mmol) in DMF (3 mL) was added to a mixture of (1-benzyloxycarbonylamino-2-methyl-propyl)-phosphonic acid monomethyl ester (1.0 g, 3.32 mmol) and 5-*tert*-butoxycarbonylamino-2-hydroxy-pentanoic acid methyl ester (865 mg, 3.5 mmol) in DMF (4 mL) under argon. DIPEA (2.28 mL, 13.3 mmol) was added dropwise and the mixture was stirred over night. Ethyl acetate was added and the mixture was washed with 10 % $KHSO_4$, satd. $NaHCO_3$ and brine and dried. Concentration under reduced pressure followed by chromathography (heptane/EtOAc, 1:1 → 1:6) gave 2-[(1-benzyloxycarbonylamino-2-methyl-propyl)-methoxy-phosphinoyloxy]-5-*tert*-butoxycarbonylamino-pentanoic acid methyl ester (1.21 g, 69 %).

(d) 2-[(1-Benzyloxycarbonylamino-2-methyl-propyl)-hydroxy-phosphinoyloxy]-5-*tert*-butoxycarbonylamino-pentanoic acid

1 M LiOH (5 mL) was added to a solution of 2-[(1-benzyloxycarbonylamino-2-methyl-propyl)-methoxy-phosphinoyloxy]-5-*tert*-butoxycarbonylamino-pentanoic acid methyl ester (187 mg, 0.35 mmol) in acetonitrile (5 mL). The mixture was stirred at 50 °C over night and concentrated under reduced pressure. The crude product was purified using

chromathography (iPrOH/conc. aq. NH_3/H_2O, 4:2:1) to yield 2-[(1-benzyloxycarbonylamino-2-methyl-propyl)-hydroxy-phosphinoyloxy]-5-*tert*-butoxycarbonylamino-pentanoic acid (180 mg, 100 %).

(e) 5-Amino-2-[(1-benzyloxycarbonylamino-2-methyl-propyl)-hydroxy-phosphinoyloxy]-pentanoic acid

TFA (3 mL) was added to a solution of 2-[(1-benzyloxycarbonylamino-2-methyl-propyl)-hydroxy-phosphinoyloxy]-5-*tert*-butoxycarbonylamino-pentanoic acid (150 mg, 0.3 mmol) in methylene chloride/acetonitrile (1:1, 15 mL). The solution was stirred for 120 min. and concentrated under reduced pressure to give the title compound as the TFA salt (174 mg, 100 %).

^{1}H NMR (500 MHz, CD_3OD): δ 1.02 (t, 6H), 1.66-2.0 (m, 4H), 2.23 (m, 1H), 2.93 (m, 2H), 3.91 (m, 1H), 4.85 (bs, 1H), 5.12 (m, 2H), 7.28-7.42 (m, 5H).

MS (+) 403.3 (M+1).

Example 2

2-[(1-Benzyloxycarbonylamino-2-methyl-propyl)-hydroxy-phosphinoyloxy]-5-guanidino-pentanoic acid

(a) 2-[(1-Benzyloxycarbonylamino-2-methyl-propyl)-hydroxy-phosphinoyloxy]-5-guanidino-pentanoic acid

A solution of S-methylisothiourea hydrogen sulfate (25 mg, 90 µmol) in 1 M NaOH (0.18 mL) was added to a solution of 5-amino-2-[(1-benzyloxycarbonylamino-2-methyl-propyl)-hydroxy-phosphinoyloxy]-pentanoic acid (36 mg, 90 µmol) and 1 M NaOH (0.18 mL) in water/MeOH (1:1, 0.4 mL). The rection mixture was stirred at 50 °C for 6 h and concentrated under reduced pressure. The crude product was purified using HPLC (0-50 % acetonitrile, 0.1% TFA in water) to give the title compound as the TFA salt (19 mg, 38 %)

^{1}H NMR (500 MHz, CD_3OD): δ 1.02 (t, 6H), 1.60-1.98 (m, 4H), 2.23 (m, 1H), 3.20 (m, 2H), 3.91 (m, 1H), 4.82 (bs, 1H), 5.11 (m, 2H), 7.26-7.42 (m, 5H).

MS (+) 445 (M+1).

Example 3

5-Amino-2-{[1-(2-benzyloxycarbonylamino-3-phenyl-propionylamino)-2-methyl-propyl]-hydroxy-phosphinoyloxy}-pentanoic acid

(a) 2-{[1-(2-Benzyloxycarbonylamino-3-phenyl-propionylamino)-2-methyl-propyl]-hydroxy-phosphinoyloxy}-5-*tert*-butoxycarbonylamino-pentanoic acid methyl ester

Thionyl chloride (49 µL, 0.67 mmol) was added dropwise to a solution of [1-(2-benzyloxycarbonylamino-3-phenyl-propionylamino)-2-methyl-propyl]-phosphonic acid (208 mg, 0.48 mmol) in DMF (5 mL) at -20 °C under argon. The mixture was stirred for 35 min at -5 °C. A solution of 5-*tert*-Butoxycarbonylamino-2-hydroxy-pentanoic acid methyl ester (166 mg, 0.67 mmol) in DMF (1 mL) was added and the mixture was stirred for 90 min at room temperature. Ethyl acetate was added and the mixture was washed with 1 M HCl, dried and concentrated under reduced pressure. The crude product was purified using chromathography ($CHCl_3$/MeOH/H_2O, 10:1:0 → 10:5:1) to give 2-{[1-(2-benzyloxycarbonylamino-3-phenyl-propionylamino)-2-methyl-propyl]-hydroxy-phosphinoyloxy}-5-*tert*-butoxycarbonylamino-pentanoic acid methyl ester (211 mg, 66 %).

(b) 2-{[1-(2-Benzyloxycarbonylamino-3-phenyl-propionylamino)-2-methyl-propyl]-hydroxy-phosphinoyloxy}-5-*tert*-butoxycarbonylamino-pentanoic acid

1 M LiOH (3.5 mL) was added to a solution of 2-{[1-(2-benzyloxycarbonylamino-3-phenyl-propionylamino)-2-methyl-propyl]-hydroxy-phosphinoyloxy}-5-*tert*-butoxycarbonylamino-pentanoic acid methyl ester (211 mg, 0.32 mmol) in acetonitrile (3.5 mL) and the mixture was stirred for 3 h. Ethyl acetate was added and the mixture was washed with 1 M HCl, dried and concentrated to give crude 2-{[1-(2-benzyloxycarbonylamino-3-phenyl-propionylamino)-2-methyl-propyl]-hydroxy-phosphinoyloxy}-5-*tert*-butoxycarbonylamino-pentanoic acid (208 mg, 100 %).

(c) 5-Amino-2-{[1-(2-benzyloxycarbonylamino-3-phenyl-propionylamino)-2-methyl-propyl]-hydroxy-phosphinoyloxy}-pentanoic acid

TFA (5 mL) was added to a solution of 2-{[1-(2-benzyloxycarbonylamino-3-phenyl-propionylamino)-2-methyl-propyl]-hydroxy-phosphinoyloxy}-5-*tert*-butoxycarbonylamino-pentanoic acid (208 mg, 0.32 mmol) in acetonitrile (5 mL) and the mixture was stirred for 90 min. The reaction mixture was concentrated under reduced pressure to give the crude title compound as the TFA salt (212 mg, 100 %). 20 mg of the crude title compound was purified using chromathography (iPrOH/conc. aq. NH_3/H_2O, 4:2:1) to give the title compound as the TFA salt (19 mg, 94 %).

^{1}H NMR (500 MHz, CD_3OD): δ 0.85-0.95 (m, 6H), 1.70-2.0 (m, 4H), 2.05-2.13 (m, 1H), 2.85-3.05 (m, 2H), 3.05-3.12 (m, 1H), 4.10 (bs, 1H), 4.55 (m, 1H), 4.90 (m, 1H), 5.09 (s, 2H), 7.20-7.35 (m, 10H).

Example 4

2-{[1-(2-Benzyloxycarbonylamino-3-phenyl-propionylamino)-2-methyl-propyl]-hydroxy-phosphinoyloxy}-5-guanidino-pentanoic acid

(a) 5-Amino-2-hydroxy-pentanoic acid methyl ester

TFA (2 mL) was added to a solution of 5-*tert*-butoxycarbonylamino-2-hydroxy-pentanoic acid methyl ester in methylene chloride (10 mL) and the mixture was stirred for 3 h and then concentrated under reduced pressure to give crude 5-amino-2-hydroxy-pentanoic acid methyl ester (1 g).

(b) 5-(Guanidino-ω, ω´-bis(*tert*-Butoxycarbonyl)-2-hydroxy-pentanoic acid methyl ester

To a solution of 5-amino-2-hydroxy-pentanoic acid methyl ester (0.5 g, 2.0 mmol) in acetonitrile (5 mL) was added *tert*-butoxycarbonylimino-pyrazol-1-yl-methyl)-carbamic acid *tert*-butyl ester (0.77g, 2.5 mmol) followed by DIPEA (0.86 mL, 5 mmol). After stirring for 60 min. ethyl acetate was added. The mixture was washed with 1 M HCl, satd. $NaHCO_3$ and brine, dried and concentrated under reduced pressure. The crude product was purified using chromathography (heptane/ethyl acetate, 1:0 → 1:3) to give 5-(guanidino-ω, ω´-bis(*tert*-butoxycarbonyl)-2-hydroxy-pentanoic acid methyl ester (0.27 g, 35 %).

(c) 2-{[1-(2-Benzyloxycarbonylamino-3-phenyl-propionylamino)-2-methyl-propyl]-hydroxy-phosphinoyloxy}-5-[guanidino-ω, ω´-bis(*tert*-Butoxycarbonyl)]-pentanoic acid methyl ester

Thionyl chloride (70 µL, 0.97 mmol) was added dropwise to a solution of [1-(2-benzyloxycarbonylamino-3-phenyl-propionylamino)-2-methyl-propyl]-phosphonic acid (301 mg, 0.69 mmol) in DMF (5 mL) at -20 °C under argon. The mixture was stirred for 20 min at -5 °C. A solution of 5-(guanidino-ω, ω´-bis(*tert*-Butoxycarbonyl)-2-hydroxy-pentanoic acid methyl ester (270 mg, 0.69 mmol) in DMF (1 mL) was added and the mixture was stirred for 180 min at room temperature. Ethyl acetate was added and the mixture was washed with 1 M HCl, dried and concentrated under reduced pressure. The crude product was purified using chromathography (toluene/ethyl acetate, 1:1 → 0:1) to give 2-{[1-(2-benzyloxycarbonylamino-3-phenyl-propionylamino)-2-methyl-propyl]-hydroxy-phosphinoyloxy}-5-[guanidino-ω, ω´-bis(*tert*-butoxycarbonyl)]-pentanoic acid methyl ester (0.27 g, 48 %).

(d) 2-{[1-(2-Benzyloxycarbonylamino-3-phenyl-propionylamino)-2-methyl-propyl]-hydroxy-phosphinoyloxy}-5-[guanidino-ω, ω´-bis(*tert*-Butoxycarbonyl)]-pentanoic acid

A solution of LiOH (42 mg, 1.0 mmol) in water (1.0 mL) was added to a solution of 2-{[1-(2-benzyloxycarbonylamino-3-phenyl-propionylamino)-2-methyl-propyl]-hydroxy-phosphinoyloxy}-5-[guanidino-ω, ω´-bis(*tert*-butoxycarbonyl)]-pentanoic acid methyl ester (160 mg, 0.2 mmol) in acetonitrile (1.0 mL) and the mixture was stirred for 15 min. Ethyl acetate was added and the mixture was washed with 1 M HCl and brine, dried and concentrated to give crude 2-{[1-(2-benzyloxycarbonylamino-3-phenyl-propionylamino)-2-methyl-propyl]-hydroxy-phosphinoyloxy}-5-[guanidino-ω, ω´-bis(*tert*-butoxycarbonyl)]-pentanoic acid (160 mg, 100 %).

(e) 2-{[1-(2-Benzyloxycarbonylamino-3-phenyl-propionylamino)-2-methyl-propyl]-hydroxy-phosphinoyloxy}-5-guanidino-pentanoic acid

TFA (2 mL) was added to a solution of 2-{[1-(2-benzyloxycarbonylamino-3-phenyl-propionylamino)-2-methyl-propyl]-hydroxy-phosphinoyloxy}-5-[guanidino-ω, ω′-bis(*tert*-butoxycarbonyl)]-pentanoic acid (160 mg, 0.2 mmol) in acetonitrile (5 mL) and the mixture was stirred for 60 min and then concentrated under reduced pressure. The crude product was purified using chromathography (iPrOH/conc. aq. NH_3/H_2O, 4:2:1) to give the title compound as the TFA salt (30 mg, 21 %).

^{1}H NMR (500 MHz, CD_3OD): δ 0.80-0.98 (m, 6H), 1.53-1.95 (m, 4H), 2.01-2.30 (m, 1H), 2.90 (m, 1H), 3.10-3.30 (m, 3H), 3.94-4.10 (m, 1H), 4.41-4.55 (m, 1H), 4.68 (m, 1H), 5.03 (m, 2H), 7.18-7.37 (m, 5H).

MS (+) 592 (M+1).

Example 5

2-Hydroxycarbamoyl-4-piperidin-4-yl-butyric acid

(a) Piperidin-4-yl-acetic acid

Pyridin-4-yl-acetic acid hydrochloride (20.0 g, 115 mmol) was added to water/25 % ammonia (125 mL:10mL). The mixture was degassed and flushed with nitrogen before addition of rhodium on activated alumina (0.45 g). The mixture was again degassed, then stirred in a hydrogen atmosphere at 50 bar for 16 h. Filtration of the reaction mixture through filter paper afforded the bulk of the catalyst which was recycled after washing with methanol. The filtrate was then filtered through Celite and concentrated to afford a white solid (19.7 g, 96 % yield).

(b) 4-Carboxymethyl-piperidine-1-carboxylic acid *tert*-butyl ester

To a solution of piperidin-4-yl-acetic acid (19.7 g, 148 mmol) in THF-water (417 mL, 1:1) was added di-tert-butyl dicarbonate (32.3 g, 148 mmol) and sodium bicarbonate (12.5 g, 148 mmol), and the reaction stirred at room temperature for 16 h. THF was then removed under reduced pressure and the aqueous phase extracted with dichloromethane and the organic layer discarded. The aqueous layer was then acidified to pH 1-2 with 1 M HCl solution and extracted with ethyl acetate. The organic phase wase washed with brine, dried

and concentrated under reduced pressure to give 4-carboxymethyl-piperidine-1-carboxylic acid *tert*-butyl ester (16.7 g, 46 %).

(c) 4-(2-Hydroxy-ethyl)-piperidine-1-carboxylic acid *tert*-butyl ester

To a solution of 4-carboxymethyl-piperidine-1-carboxylic acid *tert*-butyl ester (16.7 g, 69.0 mmol) in THF (100 mL) was added diborane (151 mL, 1.0 M solution in THF) over a period of 10 min at 0 °C. Hydrogen gas was rapidly evolved and after gas evolution had ceased the reaction was stirred at room temperature for 1 h. The reaction mixture was again cooled to 0 °C, and 1 M aqueous HCl was added dropwise to the reaction mixture with further evolution of hydrogen. Addition of HCl was continued until the evolution of hydrogen had almost ceased. The mixture was then stirred for 10 min and made basic (pH 13-14) by the addition of 1 M NaOH solution. The aqueous solution was extracted with ethyl acetate, the organic phase washed with brine, dried and concentrated under reduced pressure to yield 4-(2-hydroxy-ethyl)-piperidine-1-carboxylic acid *tert*-butyl ester (15.2 g, 97 %).

(d) 4-(2-Oxo-ethyl)-piperidine-1-carboxylic acid *tert*-butyl ester

Periodinane (36.1 g, 85.2 mmol) was added to 4-(2-hydroxy-ethyl)-piperidine-1-carboxylic acid *tert*-butyl ester (15.0 g, 65.5 mmol) in CH2Cl2 (230 mL) and stirred for 90 min. Diethyl ether (560 ml) was added and precipitates were removed by extraction with 10 % $Na_2S_2O_3$/saturated $NaHCO_3$ (1:1, 350 mL). The organic layer was washed with 0.5 M NaOH solution and brine. The organic phase was dried and concentrated under reduced pressure to yield 4-(2-Oxo-ethyl)-piperidine-1-carboxylic acid *tert*-butyl ester (8.50 g, 57 %).

(e) 4-[2-(2,2-Dimethyl-4,6-dioxo-[1,3]dioxan-5-yl)-ethyl]-piperidine-1-carboxylic acid *tert*-butyl ester.

To a solution of meldrums acid (1.68 g, 11.66 mmol) and 4-(2-oxo-ethyl)-piperidine-1-carboxylic acid *tert*-butyl ester (2.21 g, 9.72 mmol) in dichloromethane (40 mL) was added acetic acid (0.055 mL, 0.972 mmol) and piperidine (0.096 mL, 0.972 mmol). The mixture was heated at reflux for 3 h, and then allowed to attain room temperature. After being

diluted with *tert*-butyl methyl ether, the mixture was washed with $NaHCO_3$ (sat.) and brine. The organic phase was dried, filtered and concentrated. The residue was dissolved in a mixture of EtOH (40 mL) and acetic acid (20 mL). The solution was cooled to 0 °C, and $NaBH_4$ (0.554 g, 14.6 mmol) was added in portions after which the solution was allowed to stir for 30 min at rt and then acidified to pH 3 with 1 M HCl. The solution was extracted several times with dichloromethane. The combined organic phases were dried, filtered, concentrated and filtered through a pad of silica gel (dichloromethane). The solvent was evaporated to give 4-[2-(2,2-Dimethyl-4,6-dioxo-[1,3]dioxan-5-yl)-ethyl]-piperidine-1-carboxylic acid *tert*-butyl ester as a colorless oil (2.30 g, 65 %) which solidified on standing.

(f) 2-Hydroxycarbamoyl-4-piperidin-4-yl-butyric acid.

A GC-autosample vial (2 mL) equipped with a septum cap and a small stirbar was charged with 4-[2-(2,2-Dimethyl-4,6-dioxo-[1,3]dioxan-5-yl)-ethyl]-piperidine-1-carboxylic acid *tert*-butyl ester (17.8 mg, 0.05 mmol) and flushed with nitrogen. N,O-Bis(trimethylsilyl)hydroxylamine (0.2 mL) was added via syringe and the resulting solution was stirred at rt over night. The mixture was concentrated under vacuum and the residue dissolved in dichloromethane/MeOH (4:1) and applied onto a small plug of ion exchange resin (200 mg, isolute™, aminoresin), washed with dichloromethane /MeOH (4:1) and then eluted with dichloromethane/MeOH/AcOH (3:1:1). The eluate was concentrated, the residue dissolved in dichloromethane/TFA (1:1, 2 mL) and stirred for 1h at room temperature. Evaporation of the solvent gave the title compound as the TFA salt (16 mg, 93 %) as a colorless oil.

^{1}H NMR (600 MHz, CD_3OD) δ 1.21-1.40 (m, 4H), 1.53-1.62 (m, 1H), 1.80-1.99 (m, 4H), 2.90-2.98 (m, 2H), 3.06 (t, 1H), 3.32-3.39 (m, 2H).

M (+) 231 (M+1).

Example 6

N-hydroxy-2-piperidin-3-ylmethyl-malonamic acid

(a) 3-Hydroxymethyl-piperidine-1-carboxylic acid *tert*-butyl ester

3-Hydroxymethyl-piperidine (20.0 g, 0.17 mmol) in acetonitrile was treated with di-tert-butyl dicarbonate (37.9 g, 0.17 mol) and DMAP (2.13 g, 1.74 mmol). The reaction mixture was stirred at ambient temperature for 5 h and then concentrated under reduced pressure. The crude product was purified by flash chromatography (hexane/EtOAc, 70:30) to give 3-hydroxymethyl-piperidine-1-carboxylic acid *tert*-butyl ester (16.0 g, 44 %).

(b) 3-Formyl-piperidine-1-carboxylic acid tert-butyl ester

Periodinane (18.2 g, 42.9 mmol) was added to 3-hydroxymethyl-piperidine-1-carboxylic acid *tert*-butyl ester (7.10 g, 33.0 mmol) in CH_2Cl_2 (230 mL) and stirred for 90 min. Diethyl ether (230 mL) was added and precipitates were removed by extraction with 10 % $Na_2S_2O_3$/saturated $NaHCO_3$ (1:1, 230 mL). The organic layer was washed with 0.5 M NaOH solution and brine. The organic phase was dried and concentrated under reduced pressure to yield 3-Formyl-piperidine-1-carboxylic acid tert-butyl ester (6.50 g, 93 %).

(c) *N*-Hydroxy-2-piperidin-3-ylmethyl-malonamic acid

The title compound was prepared from 3-formyl-piperidine-1-carboxylic acid tert-butyl ester by the method described in Example 5. Yield: (50 %).

^{1}H NMR (600 MHz, CD_3OD) δ 1.18-1.30 (m, 1H), 1.61-1.99 (m, 6H), 2.64 (t, 1H), 2.86 (t, 1H), 3.20-3.38 (m, 3H).

M (+) 217 (M+1).

Example 7

2-(6-Amino-pyridin-3-ylmethyl)-*N*-hydroxy-malonamic acid.

The title compound was prepared from (5-Formyl-pyridin-2-yl)-carbamic acid *tert*-butyl ester by the method described in Example 5. Yield: (23 %).

^{1}H NMR (600 MHz, CD_3OD) d 2.99-3.10 (m, 2H), 3.36-4.01 (m, 1H), 6.94 (d, 1H), 7.64 (s, 1H), 7.82 (d, 1H).

M (+) 226 (M+1).

Example 8

2-(2-Amino-pyridin-4-ylmethyl)-*N*-hydroxy-malonamic acid.

(a) (4-Formyl-pyridin-2-yl)-carbamic acid *tert*-butyl ester

(4-Hydroxymethyl-pyridin-2-yl)-carbamic acid *tert*-butyl ester (1.91 g, 8.51 mmol) was dissolved in dry DMSO (10 mL) and the reaction flask immersed in a waterbath at 15 °C. Triethylamine (1.72 g, 17.0 mmol) was added followed by sulfur trioxide pyridine complex (2.41 g, 15.1 mmol). The reaction mixture was stirred for 2 h and poured onto crushed ice and the product extracted with $CHCl_3$. The organic extract was washed with water, dried concentrated under reduced pressure. The crude product was purified by flash chromatography (hexane/ EtOAc, 80:20) to give (4-Formyl-pyridin-2-yl)-carbamic acid *tert*-butyl ester (1.57 g, 83 %).

(b) 2-(2-Amino-pyridin-4-ylmethyl)-*N*-hydroxy-malonamic acid

The title compound was prepared from (4-Formyl-pyridin-2-yl)-carbamic acid *tert*-butyl ester by the method described in Example 5. Yield: (48 %).

^{1}H NMR (600 MHz, CD_3OD) δ 3.10 (dd, 1H), 3.19 (dd, 1H), 3.47 (dd, 1H), 6.77 (d, 1H), 7.82 (s, 1H), 7.71 (d, 1H).

M (+) 226 (M+1).

Example 9

2-[2-(1-*tert*-Butoxycarbonyl-piperidin-4-yl)-ethyl]-malonic acid.

To a solution of 4-[2-(2,2-Dimethyl-4,6-dioxo-[1,3]dioxan-5-yl)-ethyl]-piperidine-1-carboxylic acid *tert*-butyl ester (17.8 mg, 0.05 mmol) in acetic acid (1 mL) was added 6 M HCl (2 mL). The solution was stirred at rt over night and then concentrated to yield the title compound as the hydrochloric acid salt (15 mg, 100 %).

^{1}H NMR (600 MHz, CD_3OD) δ 1.30-1.40 (m, 4H), 1.57-1.64 (m, 1H), 1.83-1.90 (m, 1H), 1.90-1.98 (m, 1H), 3.31-3.39 (m, 2H).

M (+) 216 (M+1).

Example 10

2-[2-(1-*tert*-Butoxycarbonyl-piperidin-3-yl)-methyl]-malonic acid.

The title compound was prepared from 3-(2,2-Dimethyl-4,6-dioxo-[1,3]dioxan-5-ylmethyl)-piperidine-1-carboxylic acid *tert*-butyl ester by the method described in Example 9. Yield: (100 %).

^{1}H NMR (600 MHz, CD_3OD) δ 1.20-1.30 (m, 1H), 1.63-1.76 (m, 1H), 1.78-1.97 (m, 5H), 2.65 (t, 1H), 2.83-2.92 (m, 1H), 3.29-3.38 (m, 2H), 3.42-3.48 (m, 1H).

M (+) 202 (M+1).

Example 11

2-[2-(1-*tert*-Butoxycarbonyl-piperidin-4-yl)-methyl]-malonic acid

(a) Piperidine-1,4-dicarboxylic acid mono-*tert*-butyl ester

Piperidine-4-carboxylic acid (24.5 g, 0.19 mmol) in THF/water (1:1, 417 mL) was treated with di-tert-butyl dicarbonate (41.49 g, 0.19 mol) and sodium bicarbonate (16.0 g, 0.19 mol). The reaction mixture was stirred at ambient temperature for 16 h. The THF was then removed under reduced pressure and the aqueous phase washed with dichloromethane. The aqueous layer was then acidified to pH 1-2 with 1 M HCl solution and extracted with ethyl acetate. The organic phase was washed with brine and dried to give piperidine-1,4-dicarboxylic acid mono-*tert*-butyl ester (35.9 g, 83 %).

(b) 4-Hydroxymethyl-piperidine-1-carboxylic acid *tert*-butyl ester

To a solution of piperidine-1,4-dicarboxylic acid mono-*tert*-butyl ester (19.3 g, 84.0 mmol) in THF (100 mL) was added diborane (185 mL, 1.0 M solution in THF) over a period of 10 min at 0 °C. Hydrogen gas was rapidly evolved and after gas evolution had ceased the reaction was stirred at room temperature for 1 h. The reaction mixture was again cooled to 0 °C, and 1 M aqueous HCl was added dropwise to the reaction mixture with further evolution of hydrogen. Addition of HCl was continued until the evolution of hydrogen had almost ceased. The mixture was then stirred for 10 min and made basic (pH 13-14) by the addition of 1 M NaOH solution. The aqueous solution was extracted with ethyl acetate, the organic phase washed with brine, dried and concentrated under reduced pressure to yield 4-Hydroxymethyl-piperidine-1-carboxylic acid *tert*-butyl ester (18.12 g, 100 %).

(c) 4-Formyl-piperidine-1-carboxylic acid *tert*-butyl ester

Periodinane (26.9 g, 63.5 mmol) was added to 4-Hydroxymethyl-piperidine-1-carboxylic acid *tert*-butyl ester (10.5 g, 48.8 mmol) in CH_2Cl_2 (200 mL) and stirred for 90 min. Diethyl ether (560 mL) was added and precipitates were removed by extraction with 10 % $Na_2S_2O_3$/saturated $NaHCO_3$ (1:1, 300 mL). The organic layer was washed with 0.5 M NaOH solution and brine. The organic phase was dried and concentrated under reduced pressure. Purification using flash chromatography (hexane/EtOAc, 8:2) gave 4-Formyl-piperidine-1-carboxylic acid *tert*-butyl ester (8.5 g, 81 %).

(d) 2-[2-(1-*tert*-Butoxycarbonyl-piperidin-4-yl)-methyl]-malonic acid.

The title compound was prepared from 4-Formyl-piperidine-1-carboxylic acid *tert*-butyl ester by the method described in Example 5 and 9. Yield: (100 %).

^{1}H NMR (600 MHz, CD_3OD) δ 1.38-1.48 (m, 2H), 1.61-1.75 (m, 1H), 1.82-1.90 (m, 2H), 1.92-2.02 (m, 2H), 2.90-3.01 (m, 2H), 3.35-3.42 (m, 2H), 3.42-3.48 (m, 1H).

M (+) 202 (M+1).

Example 12

2-(6-*tert*-Butoxycarbonylamino-pyridin-3-ylmethyl)-malonic acid.

The title compound was prepared from [5-(2,2-Dimethyl-4,6-dioxo-[1,3]dioxan-5-ylmethyl)-pyridin-2-yl]-carbamic acid *tert*-butyl ester by the method described in Example 9. Yield: (100 %).

^{1}H NMR (600 MHz, CD_3OD) δ 3.08 (d, 2H), 3.66 (t, 1H), 6.98 (d, 1H), 7.73 (s, 1H), 7.92 (d, 1H).

M (+) 211 (M+1).

Example 13

2-(2-*tert*-Butoxycarbonylamino-pyridin-4-ylmethyl)-malonic acid.

The title compound was prepared from [4-(2,2-Dimethyl-4,6-dioxo-[1,3]dioxan-5-ylmethyl)-pyridin-2-yl]-carbamic acid *tert*-butyl ester by the method described in Example 9. Yield: (100 %).

^{1}H NMR (600 MHz, CD_3OD) δ 3.10 (d, 2H), 3.79 (t, 1H), 6.84 (d, 1H), 7.92 (s, 1H), 7.77 (d, 1H).

M (+) 211 (M+1).

Example 14

2-(2-Amino-pyridin-4-ylmethyl)-succinic acid

(a) 2-(2-*tert*-Butoxycarbonylamino-pyridin-4-ylmethylene)-succinic acid 4-benzyl ester 1-*tert*-butyl ester

Butyllithium (1.6 M in hexane, 14.8 ml, 23.7 mmol) was added dropwise to a solution of 2-(diethoxy-phosphoryl)-succinic acid 4-benzyl ester 1-*tert*-butyl ester (9.50 g, 23.7 mmol in THF (75 mL) at 0 °C under nitrogen. After stirring at 0 °C for 1 h, the solution was transferred to a solution of (4-Formyl-pyridin-2-yl)-carbamic acid *tert*-butyl ester (3. 70 g, 16.6 mmol) in THF (75 mL). The resulting reaction mixture was stirred at 0 °C for 1 h before being allowed to warm to 25 °C, and the mixture was stirred overnight. Water (400 mL) was added and the product extracted with CH_2Cl_2 (3x50 mL). The combined organic layers were dried and concentrated. Flash chromatography (hexane/EtOAc, 4:1) gave 2-(2-*tert*-Butoxycarbonylamino-pyridin-4-ylmethylene)-succinic acid 4-benzyl ester 1-*tert*-butyl ester 4.30 g (55 %).

(b) 2-(2-*tert*-Butoxycarbonylamino-pyridin-4-ylmethyl)-succinic acid 1-*tert*-butyl ester

2-(2-*tert*-Butoxycarbonylamino-pyridin-4-ylmethylene)-succinic acid 4-benzyl ester 1-*tert*-butyl ester (2.81 g, 7.60 mmol) and Pd/C (10 %, 400 mg) were suspended in EtOH and hydrogenated at 41 atm. and 28 °C for 3 days. The catalyst was removed from the reaction mixture by filtration. The catalyst was washed with EtOH (96 %). 1 M K_2CO_3 (30 mL) was added to the filtrate followed by addition of water (50 mL). After 2 days the reaction mixture was evaporated to ca 80 mL, then brine (10 mL) was added and the reaction mixture extracted with ether. The aqueous phase was acidified to pH=3 and extracted with chloroform. Methanol (25 mL) was added and the reaction mixture was dried (Na_2SO_4 + $CaSO_4$) and filtered to give 2-(2-*tert*-butoxycarbonylamino-pyridin-4-ylmethyl)-succinic acid 1-*tert*-butyl ester (1.90 g, 83 %).

(c) 2-(2-Amino-pyridin-4-ylmethyl)-succinic acid

To a solution of 2-(2-*tert*-butoxycarbonylamino-pyridin-4-ylmethyl)-succinic acid 1-*tert*-butyl ester (164 mg, 0.43 mmol) in methylene chloride (1.5 mL) was added TFA (1.5 mL). The reaction mixture was stirred for 2.5 h and then concentrated under reduced pressure. The residue was lyophilized to give the title compound as the TFA salt (126mg, 87 %)

^{1}H NMR (500 MHz, D_2O): δ 2.58-2.80 (m, 2H), 2.88-3.07 (m, 2H), 3.13-3.26 (m, 1H), 6.79-6.84 (dd, 1H), 6.84-6.88 (s, 1H), 7.69-7.75 (d, 1H).

MS (+) 225 (M+1).

Example 15

trans-2-(4-Amino-cyclohexylmethyl)-succinic acid

(a) 4-[*N*-(*tert*-Butoxycarbonyl)amino]-cyclohexane carboxylic acid

To a solution of *cis*-4-aminocyclohexane carboxylic acid (9.90 g, 69.0 mmol) in water (120 mL) and dioxane (120 mL) was added KOH (3.73 g, 56 mmol) followed by di-*tert*-butyl dicarbonate (15.3 g, 70.0 mmol). The reaction mixture was stirred at room temperature overnight. Water was added and the product was extracted with $CHCl_3$. The combined organic extracts were washed with water, dried and concentrated under reduced pressure to give 4-[*N*-(*tert*-butoxycarbonyl)amino]-cyclohexane carboxylic acid (14.1 g, 84 %).

(b) [4-(Methoxy-methyl-carbamoyl)-cyclohexyl]-carbamic acid *tert*-butyl ester

A solution of 4-[*N*-(*tert*-butoxycarbonyl)amino]-cyclohexane carboxylic acid (11.95 g, 49.0 mmol), *O,N*-dimethylhydroxylamine (4.88 g, 50.0 mmol), DCC (9.60 g, 50 mmol) and triethylamine (5.06 g, 50.0 mmol) in DMF (150 mL) was stirred at room temperature overnight. Water (500 mL) was added and the mixture was extracted with $CHCl_3$. The organic phase was washed with water, dried and concentrated under reduced pressure. Purification by flash chromatography (hexane/EtOAc 1:1) gave [4-(methoxy-methyl-carbamoyl)-cyclohexyl]-carbamic acid *tert*-butyl ester (8.50 g, 61 %).

(c) (4-Formyl-cyclohexyl)-carbamic acid *tert*-butyl ester

[4-(Methoxy-methyl-carbamoyl)-cyclohexyl]-carbamic acid *tert*-butyl ester (7.50 g, 26.2 mmol) in dry ether (150 ml) was reduced with an excess $LiAlH_4$. The reaction mixture was quenched by careful addition of water and extracted with $CHCl_3$. The mixture was dried and concentrated under reduced pressure to give (4-formyl-cyclohexyl)-carbamic acid *tert*-butyl ester (6.30 g, 93 %).

(d) trans-[4-(Benzylimino-methyl)-cyclohexyl]-carbamic acid tert-butyl ester

A mixture of (4-Formyl-cyclohexyl)-carbamic acid *tert*-butyl ester (3.80 g, 16.7 mmol), benzylamine (1.82 g, 16.7 mmol), acetic acid (0.01 g, 16.7 mmol) and anhydrous magnesium sulfate (4.01 g, 33.3 mmol) in methylene chloride (20 mL) was stirred for 5 days. The mixture was filtered through Celite and concentrated under reduced pressure to give trans-[4-(benzylimino-methyl)-cyclohexyl]-carbamic acid tert-butyl ester (5.10 g, 97 %) as a 97:3 *trans:cis* mixture.

(e) trans-(4-Formyl-cyclohexyl)-carbamic acid *tert*-butyl ester

A solution of trans-[4-(benzylimino-methyl)-cyclohexyl]-carbamic acid tert-butyl ester (2.50 g, 8.00 mmol) and oxalic acid (0.80 g) in water/THF (50 mL, 1:1) was stirred for 10 h at room temperature. The reaction mixture was concentrated under reduced pressure and methylene chloride (50 mL) was added to the residue. The organic phase was dried and concentrated under reduced pressure to give trans-(4-Formyl-cyclohexyl)-carbamic acid *tert*-butyl ester (1.3 g, 80 %).

(f) trans 2-(4-*tert*-Butoxycarbonylamino-cyclohexylmethylene)-succinic acid 4-benzyl ester 1-*tert*-butyl ester

Butyllithium (1.6 M in hexane, 5.0 ml, 8.00 mmol) was added dropwise to a solution of 2-(diethoxy-phosphoryl)-succinic acid 4-benzyl ester 1-*tert*-butyl ester (3.21 g, 8.00 mmol) in THF (25 mL) at 0 °C under nitrogen. After stirring at 0 °C for 1 h, the solution was transferred to a solution of trans-(4-Formyl-cyclohexyl)-carbamic acid *tert*-butyl ester (1.30 g, 5.72 mmol) in THF (10 mL). The resulting mixture was stirred at 0 °C for 1 h and at room temperature overnight. Water was added and the product extracted with CH_2Cl_2. The organic phase was dried and concentrated under reduced pressure. Flash chromatography

(hexane/EtOAc, 80:20) gave trans-2-(4-*tert*-Butoxycarbonylamino-cyclohexylmethylene)-succinic acid 4-benzyl ester 1-*tert*-butyl ester (1.10 g)

(g) trans-2-(4-*tert*-Butoxycarbonylamino-cyclohexylmethyl)-succinic acid 1-*tert*-butyl ester

A solution of trans-2-(4-*tert*-Butoxycarbonylamino-cyclohexylmethylene)-succinic acid 4-benzyl ester 1-*tert*-butyl ester (243 mg, 0.51 mmol) and palladium (5 % on charcoal) in ethanol (15 mL) was hydrogenated at 4 bar for 3 h. The catalyst was removed from the reaction mixture by filtration. The catalyst was washed with ethanol and the solution was concentrated under reduced pressure to give crude trans-2-(4-*tert*-Butoxycarbonylamino-cyclohexylmethyl)-succinic acid 1-*tert*-butyl ester (217 mg, >100 %).

(h) trans-2-(4-Amino-cyclohexylmethyl)-succinic acid

To a solution of trans-2-(4-*tert*-Butoxycarbonylamino-cyclohexylmethyl)-succinic acid 1-*tert*-butyl ester (200 mg, 0.52 mmol) in methylene chloride (1.32 g, 15.6 mmol) was added triethylsilane (150 mg, 1.30 mmol) followed by TFA (770 mg, 6.75 mmol). The reaction mixture was stirred for 2.5 h and then concentrated under reduced pressure. Purification by HPLC (0-80 % acetonitrile, 0.1 % TFA in water) gave the title compound as the TFA salt (60 mg, 34 %)

^{1}H NMR (500 MHz, D_2O): δ 0.99-1.11 (m, 2H), 1.30-1.46 (m, 4H), 1.54-1.62 (m, 1H), 1.79-1.86 (m, 1H), 1.89-1.96 (m, 1H), 1.99-2.06 (m, 2H), 2.58-2.71 (m, 2H), 2.85-2.95 (m, 1H), 3.08-3.17 (m, 1H).

MS (+) 230 (M+1).

Example 16

2-(6-Amino-pyridin-3-ylmethyl)-*N*-benzyl-*N*-hydroxy-succinamic acid

(a) *N*-Benzyl-*N*-benzyloxy-2-(6-*tert*-butoxycarbonylamino-pyridin-3-ylmethyl)-succinamic acid *tert*-butyl ester

To a solution of 2-(2-*tert*-butoxycarbonylamino-pyridin-4-ylmethyl)-succinic acid 1-*tert*-butyl ester (0.67 g, 1.76 mmol) in CH_2Cl_2 (25 mL) was added *N*-benzyl-*N*-benzyloxy amine (0.42 g, 1.94 mmol), DCC (0.40 g, 1.94 mmol) and DMAP (0.02 g, 0.17 mmol) and

the mixture was stirred overnight. Water was added and the mixture was extracted with CH_2Cl_2. Th organic phase was dried and filtered and the residue purified by flash chromatography (hexane/EtOAc, 4:1) to give *N*-Benzyl-*N*-benzyloxy-2-(6-*tert*-butoxycarbonylamino-pyridin-3-ylmethyl)-succinamic acid *tert*-butyl ester (0.51 g, 50 %).

(b) 2-(6-Amino-pyridin-3-ylmethyl)-*N*-benzyl-*N*-benzyloxy-succinamic acid

To a solution of *N*-Benzyl-*N*-benzyloxy-2-(6-*tert*-butoxycarbonylamino-pyridin-3-ylmethyl)-succinamic acid *tert*-butyl ester (1.0 g, 1.7 mmol) in methylene chloride (10 mL) was added TFA (4 mL) at 0 °C. The reaction mixture was stirred for 4 hs and then concentrated under reduced pressure to give crude 2-(6-Amino-pyridin-3-ylmethyl)-*N*-benzyl-*N*-benzyloxy-succinamic acid as the TFA salt (0.9 g, 100 %).

(c) 2-(6-Amino-pyridin-3-ylmethyl)-*N*-benzyl-*N*-hydroxy-succinamic acid

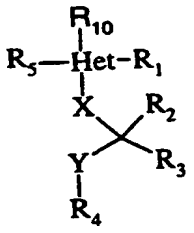
A solution of 2-(6-Amino-pyridin-3-ylmethyl)-*N*-benzyl-*N*-benzyloxy-succinamic acid (0.9 g, 1.7 mmol) and palladium (0.5g, 5 % on charcoal) in methanol (100 mL) was hydrogenated at 1 bar for 2 h. The reaction mixture was filtered and concentrated under reduced pressure. The residue was purified by flash chromatography ($CHCl_3$/MeOH/H_2O, 10:5:1) to give the title compound (123 mg, 22 %).

^{1}H NMR (600 MHz, CD_3OD): δ 2.50-3.03 (m, 5H), 4.72 (q, 2H), 6.65 (d, 1H), 7.18-7.31 (m, 6H), 7.53 (d, 1H), 7.65 (s, 1H).

MS (+) 330 (M+1).

CLAIMS

1. A compound of formula I



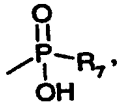
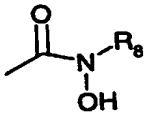
(I)

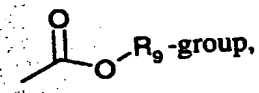
or a pharmaceutically acceptable salt thereof, wherein

R_1 represents H, OH, halogen, C_1-C_6 alkyl, C_1-C_6 alkylaryl, C_1-C_6 alkoxy, cyano, NO_2, SH och $N(R_8)_2$ or CO-C_1-C_6 alkyl,

R_2 represents H, OH, halogen, or C_1-C_6 alkyl,

R_3 represents $COOR_6$, SO_2R_6, SO_3R_6, $P{=}O(OR_6)_2$, $B(OR_6)_2$, $P{=}OR_6(OR_6)$, tetrazole or any carboxylic acid isostere,

R_4 represents  , or a  -group, or a

 ,

R_5 represents H, OH, halogen, C_1-C_6 alkyl, C_1-C_6 alkylaryl, C_1-C_6 alkoxy, cyano, NO_2, SH och $N(R_8)_2$ or CO-C_1-C_6 alkyl,

R_6 represents H, or C_1-C_6 alkyl, C_1-C_6 alkylaryl, or aryl

R_7 represents a dipeptid or an aminoacid residue, both optionally N-protected,

R_8 represents H, C_1-C_6 alkyl, or C_1-C_6 alkylaryl,

R_9 represents H, or C_1-C_6 alkyl, C_1-C_6 alkylaryl, or aryl

R_{10} represents H, OH, halogen, C_1-C_6 alkyl, C_1-C_6 alkylaryl, C_1-C_6 alkoxy, cyano, NO_2, SH och $N(R_8)_2$ or CO-C_1-C_6 alkyl,

X represents O, S, CH_2, CH_2CH_2, $CH_2CH_2CH_2$, NH, CH(Z) or N(Z),

Y represents O, CH_2, or CH(Z), or a single bond,

Z represents C_1-C_6 alkyl, or C_1-C_6 alkylaryl, and

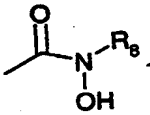
Het represents a 4-, 5-, or 6-membered aromatic or alifatic heterocyclic group containing at least one nitrogen, oxygen or sulphur atom, a 4-, 5-, or 6-membered aromatic or alifatic carbocyclic group or a single bond.

2. A compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein

R_1 represents H, or NH_2,

R_2 represents H,

R_3 represents $COOR_6$,

R_4 represents a  -group,

R_5 represents H, or NH_2,

R_6 represents H, or C_1-C_6 alkyl,

R_8 represents H, C_1-C_6 alkyl, or C_1-C_6 alkylaryl,

R_{10} represents H, or NH_2,

X represents CH_2, CH_2CH_2, or $CH_2CH_2CH_2$,

Y represents a single bond, and

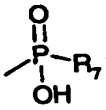
Het represents pyridyl or piperidinyl.

3. A compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein

R_1 represents NH_2, or a guanidino group,

R_2 represents H,

R_3 respesents $COOR_6$,

R_4 represents a  -group,

R_5 represents NH_2, or a guanidino group,

R_6 represents H, or C_1-C_6 alkyl,

R_7 represents a dipeptid or an aminoacid residue, both optionally N-protected,

R_{10} represents NH_2, or a guanidino group,

X represents CH_2, CH_2CH_2, or $CH_2CH_2CH_2$,

Y represents O, and

Het represents a single bond.

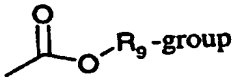
4. A compound according to claim 1, or a pharmaceutically acceptable salt thereof,

wherein

R_1 represents H, or NH_2,

R_2 represents H,

R_3 represents $COOR_6$,

R_4 represents a  -group

R_5 represents H, or NH_2,

R_6 represents H, or C_1-C_6 alkyl,

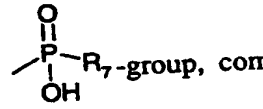
R_9 represents H, or C_1-C_6 alkyl,

R_{10} represents H, or NH_2,

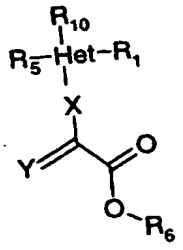
X represents CH_2, or CH_2CH_2,

Y represents CH_2, or a single bond, and

Het represents pyridyl or piperidinyl.

5. A process for the preparation of a compound according to any of claims 1-4, wherein R_1, R_5, R_6, R_7, R_{10}, X, Y, Z and Het are as defined above and R_2 is H, R3 is $COOR_6$ and R_4 is a  -group, comprising the following step,

reacting a compound of formula VI

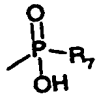


VI

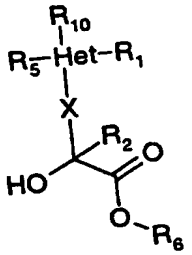
wherein R_1, R_3, R_5, R_{10}, X, Y, and Het are as defined in claim 1, with a compound of the formula IX

$$R_7PO_2H_2 \qquad IX$$

wherein R_7 is as defined in claim 1 in the presence of a suitable reagent, such as BTSP or HMDS, under standard conditions.

6. A process for the preparation of a compound according to any of claims 1-4, wherein R_1, R_2, R_3, R_5, R_6, R_7, R_{10}, X, Z and Het are as defined above, Y is O and R_4 is a  -group, comprising the following step;

reacting a compound of formula XII

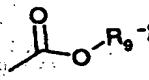


XII

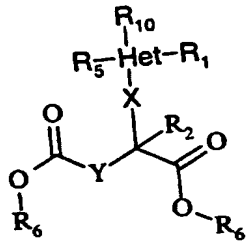
with a compound of the formula XXIII

$R_7PO_3H_2$ XIII

wherein R_7 is a defined in claim 1, in the presence of suitable coupling reagents such a DCC/DMAP, PyBop/DIPEA or $SOCl_2$, under standard conditions.

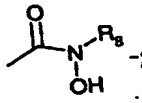
7. A process for the preparation of a compound according to any of claims 1-4, wherein R_1, R_2, R_5, R_6, R_9, R_{10}, X, Y, Z and Het are as defined above, R_3 is $COOR_6$ and R_4 is a  -group, comprising the step;

hydrolyzing a compound of formula XV

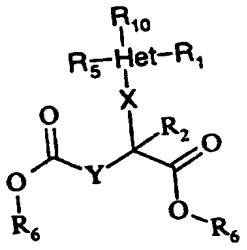


XV

under standard conditions, for example by using aqueous base or aqueous acid.

8. A process for the preparation of a compound according to any of claims 1-4, wherein R_1, R_2, R_5, R_6, R_8, R_{10}, X, Z and Het are as defined above, Y is a single bond, R_3 is $COOR_6$, and R_4 is a  -group, comprising the step;

reacting a compound of formula XV



XV

wherein R_1, R_2, R_6, R_{10}, X, Y, and Het are as defined in claim 1, with a compound of the general formula XVI

$$HR_8NOH \qquad \text{XVI}$$

wherein R_8 is as defined in claim 1, in the presence of suitable reagents, such as DCC/DMAP, under standard conditions.

9. A pharmaceutical formulation containing a compound according to any one of claims 1 to 4 as active ingredient in combination with a pharmaceutically acceptable diluent or carrier.

10. Use of a compound according to any one of claims 1 to 4 in therapy.

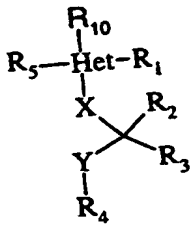
11. Use of a compound according to any one of claims 1 to 4 for the manufacture of a medicament for the inhibition of carboxypeptidase U.

12. A method for treatment or prophylaxis of conditions associated with inhibition of carboxypeptidase U, comprising administering to a mammal, including man, in need of such treatment an effective amount of a compound as defined in any of claims 1-4.

13. A pharmaceutical formulation for use in the treatment or prophylaxis of conditions associated with inhibition of carboxypeptidase U, comprising a compound as defined in any of claims 1-4 in combination with a pharmaceutically acceptable carrier or diluent.

ABSTRACT

The present invention relates to compounds of the formula (I) , and pharmaceutically acceptable salts thereof which inhibit carboxypeptidase U and thus can be used in the prevention and treatment of diseases associated with carboxypeptidase U. In further aspects, the invention relates to compounds of the invention for use in therapy; to processes for preparation of such new compounds; to pharmaceutical compositions containing at least one compound of the invention, or a pharmaceutically acceptable salt thereof, as active ingredient; and to the use of the active compounds in the manufacture of medicaments for the medical use indicated above.



(I)